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In vivo MRI-based 3D Mechanical Stress–Strain Profiles of Carotid Plaques with Juxtaluminal Plaque Haemorrhage: An Exploratory Study for the Mechanism of Subsequent Cerebrovascular Events

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Abstract *Objectives:* Atherosclerotic plaque features, such as fibrous cap erosion, ulceration and rupture and presence of haemorrhage in carotid plaque are two important characteristics associated with subsequent cerebrovascular events and juxtaluminal haemorrhage/thrombus (JLH/T) indicates these two high-risk characteristics. This study aims to investigate the association between JLH/T and subsequent events in patients suffering from transient ischaemic attack (TIA). Three-dimensional mechanical analysis was employed to represent the critical mechanical stress (P-CStress) and stretch (P-CStretch) within the plaque.
Methods: Fifty TIA patients with mild-to-moderate carotid stenosis (30–69%) underwent high-resolution magnetic resonance imaging (MRI) within 72 h of the acute event and eight were excluded from the analysis due to various reasons. A total of 21 patients were found to have JLH/T in the carotid plaque and 21 did not (N-JLH/T). During a 2-year follow-up period, 11 (52.4%) patients in the JLH/T group experienced recurrent events and none in the N-JLH/T group. Three-dimensional plaque structure was reconstructed based on the *in vivo* MRI for the mechanical analysis.
Results: P-CStress of both groups was comparable (N-JLH/T: 174.45 $\pm$ 63.96 kPa vs. JLH/T: 212.60 $\pm$ 89.54 kPa; $p = 0.120$), but P-CStretch of JLH/T was significantly bigger than that of N-JLH/T (N-JLH/T: 1.21 $\pm$ 0.08 vs. JLH/T: 2.10 $\pm$ 0.53; $p < 0.0001$). Moreover, there were much bigger variations in stress and stretch of the JLH/T group during one cardiac cycle than in those of N-JLH/T group.

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Conclusions: In vivo MRI-depicted JLH/T might be a high risk factor initiating recurrent events, as big deformation appearing around the rupture site might prevent healing and tear the haemorrhage/thrombus away from the host structure and prompt further thrombo-embolic events.

Patients suffering from a transient ischaemic attack (TIA) are at high risk of a stroke or recurrent TIA, with about half of all recurrent events during the 7 days after a TIA occurring within the first 24 h.[1] Large trials have shown that carotid endarterectomy benefits patients with high-grade carotid stenosis,[2] but the risk-to-benefit ratio is less clear-cut for symptomatic patients with moderate stenosis (50–69%). Therefore, degree of stenosis as the current diagnostic criterion is insufficient to refine risk stratification of TIA patients with moderate stenosis. Identification of new risk factors within this group could have a great benefit.

Plaque haemorrhage (PH) and fibrous cap (FC) rupture have been regarded as emerging risk characteristics associated with subsequent events. It has been observed that these two characteristics had a much wider prevalence in acutely symptomatic patients than in asymptomatic patients[3,4] and the percentage volume of PH was higher in the TIA patient than the asymptomatic patient.[5] Compared with those with thick FCs, patients with ruptured caps were 23 times more likely to have had a recent TIA or stroke.[6] The risk nature of these two characteristics in the symptomatic patient group has been validated by various prospective studies. A higher risk for subsequent stroke was found if angiographic evidence of plaque ulcer was demonstrated in patients with high-grade ($\geq$70%) stenosis.[7] Fifteen out of 66 recurrent events were associated with carotid intraplaque haemorrhage, whereas only two recurrent events occurred in the absence of intraplaque haemorrhage in symptomatic patients with high-grade stenotic plaques.[8] Similar results were obtained from symptomatic patients with mild-to-moderate (30–69%) stenosis.[9] More recently, in a prospective study including 61 TIA patients, it was found that presence of FC rupture and PH were closely associated with subsequent cerebrovascular events (hazard ratios (HRs) are 7.39 and 5.85, respectively).[10] Studies involving asymptomatic patients also reveal the risk nature of FC rupture and PH. It was found that presence of thin or ruptured FC and PH were associated with cerebrovascular events (HRs are 17.0 and 5.2, respectively) in asymptomatic patients ($n = 154$; stenosis: 50–79%).[11] This conclusion was confirmed by the association of magnetic resonance image (MRI)-depicted PH and subsequent cerebrovasuclar events (HR = 3.59) in asymptomatic patients with moderate carotid stenosis (50–70%).[12]

At the time of FC rupture/erosion or ulceration, the underlying prothrombotic lipid-rich necrotic material will be exposed to the bloodstream, which may lead to thrombus formation at the site of FC rupture; this is known as juxtaluminal thrombus.[13] Therefore, juxtaluminal haemorrhage/thrombus (JLH/T) represents FC erosion, ulceration or rupture. The blood clot may further increase the chance of thrombo-embolic events. However, its clinical relevance has been hardly investigated. This prospective study aimed to investigate the association between JLH/T and subsequent cerebrovascular events. Three-dimensional (3D) simulation was used to analyse the critical mechanical conditions within the plaque structure to shed light on the possible mechanism of thrombotic events, as FC rupture possibly occurs when the extra loading exceeds its material strength.[14,15]

Methods

MR image acquisition

A total of 50 patients were recruited for this study. The protocol was reviewed and approved by the regional research ethics committee and all patients gave written informed consent. The carotid artery was imaged within 72 h of the onset of ischaemic cerebrovascular symptoms in a 1.5-T MRI system (Sigma HDx GE Healthcare, Waukesha, WI, USA) with a four-channel phased-array neck coil (PACC, Machnet BV, Elde, the Netherlands). Movement artefact was minimised using a dedicated vacuum-based head-restraint system (VAC-LOK Cushion, Oncology Systems Limited, UK) to fix the head and neck in a comfortable position and allow close apposition of the surface coils. After an initial coronal localiser sequence, axial two-dimensional (2D) time-of-flight (TOF) MR angiography was performed to identify the location of the carotid bifurcation and the region of maximum stenosis. Axial images (3 mm thick) were acquired to ensure that the entire plaque on the previously symptomatic side was imaged. The following electrocardiography (ECG)-gated fast-spin echo-pulse sequences were used to delineate various plaque components, such as FC, lipid-rich necrotic core (LRNC) and PH: T_1-weighted (repetition time/echo time: 1 $\times$ RR/7.8 ms) with fat saturation, proton density (PD)-weighted (repetition time/echo time: 2 $\times$ RR/7.8 ms) with fat saturation, T_2-weighted (repetition time/echo time: 2 $\times$ RR/85 ms) with fat saturation and short tau inversion recovery (STIR) (repetition time/echo time/inversion time: 2 $\times$ RR/42 ms/150 ms). The field of view was 10 $\times$ 10 cm^2 and matrix size 256 $\times$ 256. The in-plane spatial resolution achieved was 0.39 $\times$ 0.39 mm^2. This MR protocol has been used previously for carotid plaque imaging.[16]

Following the event, it was ensured that patients were on the best medical therapy, that is, anti-platelets, cholesterol-lowering medication and anti-hypertensive medication (if required). They were followed up prospectively for 2 years. The clinical end point for the study was a cerebrovascular event, including stroke or TIA in the region supplied by the index carotid artery, or operation on the index artery to prevent a stroke. The date of symptoms

of clinical end points was ascertained by review of hospital records and confirmed by patient interviews.

The criteria for inclusion in the study were:

- internal carotid artery (ICA) stenosis of $\geq$30–69% on duplex imaging during screening assessment;
- sufficient MR-image quality to identify the lumen wall and outer boundary of the arterial wall; the image quality was rated before review by using a previously-published five-point scale;[17] images with quality >4 were included for quantitative analysis; and
- normal heart rhythm, confirmed by 24-h Holter monitoring and normal transthoracic echocardiography in patients in whom a cause of stroke other than carotid artery disease was suspected.

Exclusion criteria included:

- previous carotid endarterectomy (CEA) of the symptomatic carotid artery;
- cardiac arrhythmias;
- known coagulation/clotting disorder responsible for patient's symptoms;
- patients undergoing thrombolysis following the acute cerebrovascular event;
- clinical contraindications to MRI, for example, inner ear implants, and pacemaker.

MR image analysis

Plaque components such as LRNC and PH were manually delineated by experienced MR readers in agreement, using CMRTools (London, UK) with images of the five contrast weightings and confirmed by a consultant neuroradiologist using previously-published criteria.[4,18] The appearance of FC was categorised as ruptured or intact based on the definitions:[6] (1) disrupted or no visible dark band adjacent to the lumen on TOF images and irregular lumen boundary on TOF, T_1-, PD and T_2-weighted images (Fig. 1, 1st row) and (2) smooth lumen surface on TOF and T_1-, PD- and T_2-weighted images (Fig. 1, 2nd row). The JLH/T was judged according to the location of haemorrhage associated with the region of FC discontinuity.[13] If JLH/T was not found in any MR slice, the plaque would be classified as without juxtaluminal haemorrhage/thrombus (N-JLH/T). Validated by histology, MRI can identify and differentiate between intraplaque haemorrhage and JLH/T with an accuracy of 96%.[13]

3D finite element analysis

The 3D plaque geometry reconstruction was based on MRI segmentation. In the *in vivo* condition, the artery is axially stretched and pressurised; thus, axial and circumferential shrinking was applied to generate the start shape for the computational simulation.[15] Advanced plaques have complex irregular geometries with component inclusions; a component-fitting mesh-generation technique was developed to generate structured mesh for these models.[15,19] In brief, the 3D geometry was divided into hundreds of small six-face volumes and the entire structure was meshed using hexahedron elements to deal with models involving highly non-linear material properties and large deformations.

The deformation of each atherosclerotic component is governed by kinetic equation,

$$\rho V_{i,tt} = \sigma_{ij,j} (i,j = 1,2,3; \text{ sum over } j)$$

where V and σ are the displacement vector and stress tensor, respectively, ρ is the density of the component and t stands for time. The plaque components were assumed to be hyperelastic, as described by modified Mooney–Rivlin strain energy density function,

$$W = c_1(I_1 - 3) + D_1 \exp[D_2(I_1 - 3) - 1]$$

where I_1 is the first strain invariant and c_1, D_1 and D_2 are material parameters, which are from earlier studies.[20] The pulsatile blood pressure for each patient, measured before MR imaging, was used as the loading condition for the dynamic simulation. Maximum principle stress and stretch were computed using finite element method (FEM) in ADINA8.6.1 (ADINA; R&D, Inc., MA, USA) (A brief

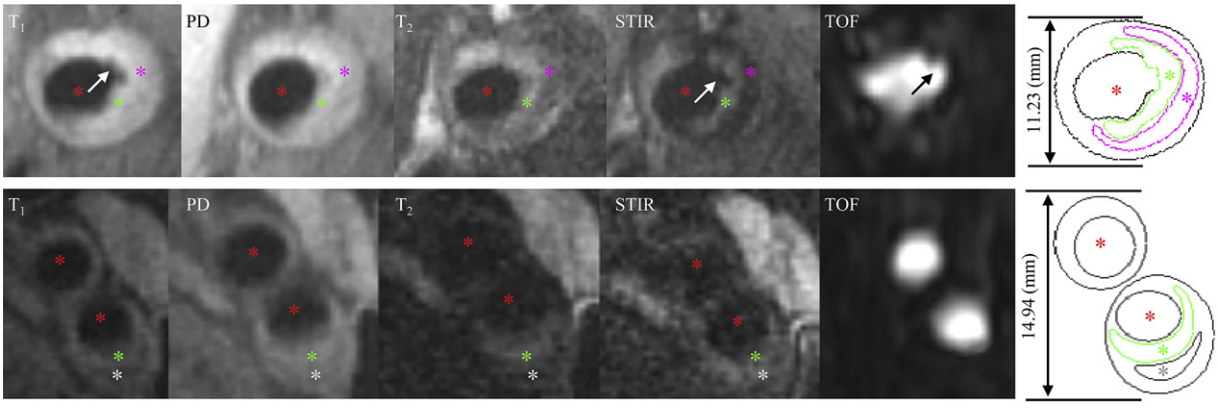

Figure 1 High resolution, multi sequence MR-image showing plaques with juxtaluminal plaque haemorrhage (the 1st row) and intraplaque haemorrhage (the 2nd row). The corresponding segmented contour is shown in the last column. Arrow head points to the location of fibrous cap rupture and exposure of haemorrhage/thrombosis. Red asterisk: lumen; Green asterisk and line: haemorrhage; Magenta asterisk and line: lipid core; Grey asterisk and black line: calcium, lumen and wall contours.

Table 1 Patient demographics.

	N-JLH/T (n = 21)	JLH/T (n = 21)	p value
Male, n (%)	10(47.6)	15(71.4)	0.21[a]
Age (Mean ± SD)	74.07 ± 9.67	72.64 ± 12.57	0.54[b]
Diastolic blood pressure (Mean ± SD; mmHg)	82.48 ± 9.95	79.00 ± 15.41	0.39[b]
Systolic blood pressure (Mean ± SD; mmHg)	145.86 ± 23.96	140.43 ± 22.47	0.45[b]
Heart rate (Median [IQR])	76(71, 82)	72(71,80)	0.53[c]
Hypertension, n (%)	14(66.7)	17(81.0)	0.48[a]
Diabetes, n (%)	2(9.5)	2(9.5)	1.39[a]
Renal impairment, n (%)	1(4.8)	3(14.3)	0.61[a]
Ischaemic heart disease, n (%)	1(4.8)	3(14.3)	0.61[a]
Peripheral vascular disease, n (%)	1(4.8)	4(19.0)	0.34[a]
Coronary artery disease, n (%)	3(14.29)	4(19.0)	1.00[a]
Previous TIA/Stroke, n (%)	3(14.29)	7(33.3)	0.28[a]
Statin used before recruitment, n (%)	10 (47.6)	15 (71.4)	0.21[a]
Aspirin used before recruitment, n (%)	8 (38.1)	10 (47.6)	0.76[a]
Stenosis % (Median [IQR])	47(41, 51)	50(48, 66)	0.05[c]
Days of follow-up (Median [IQR])	508(342, 696)	262(10, 610)	0.08[c]

Stenosis: ECST defined.
[a] Two-sided p value using Fisher's exact test.
[b] Two-tailed p value using unpaired t-test.
[c] Two-tailed p value using Mann–Whitney test.

introduction of FEM can be found in the reference).[21] The critical mechanical stress and stretch (P-CStress and P-CStretch) were defined as the maxima of stress and stretch over the diseased region.

In this study, 3D structure-only analysis was performed. Although shear stress plays an important role in atherosclerotic disease initiation and progression, for plaque rupture, the stress in the structure is believed to play a more important role, as it would be 10 000 times the magnitude of shear stress;[19] therefore, shear stress analysis was not included in this study. Moreover, for mild-to-moderate stenotic plaques, the stresses obtained from a structure-only model and a model considering fluid–structure interaction are almost the same.[22] Therefore, ignoring the blood flow will not affect the accuracy of P-CStress and P-CStretch.

Statistical analysis

For the data set not passing the normality test (Shapiro–Wilk test), the two-tailed Mann–Whitney test was used for the statistical analysis; otherwise, the two-tailed Student's t-test was used. The two-sided Fisher's exact test was used to analyse the difference in contingency tables. The statistical analysis was performed in Instat3.06 (GraphPad Software Inc., CA, USA). A significant difference was assumed if $p < 0.05$.

Results

Eight patients were excluded from the analysis for the following reasons: plaque could not be detected in two patients; two patients did not have enough plaque coverage; one patient had very little disease with intraluminal thrombus; MRI scan failed in one patient; and image quality was low in two patients. In total, 21 patients were identified as having plaques with JLH/T and 21 were N-JLH/T. As shown in Table 1, there is no significant difference between any pair of patient demographics. During the follow-up period, in the JLH/T group, 11 patients (52.4%) had recurrent cerebrovascular events in the territory of the index carotid artery and no patients in the N-JLH/T group had an ischaemic event (p = 0.0003). Kaplan–Meyer plots for the two groups are shown in Fig. 2. Log-rank analysis showed that time to event was significantly higher in the JLH/T group compared with the N-JLH/T group (p = 0.0001).

As shown in Fig. 3(A), due to the missing FC, the underlying haemorrhage (marked in green) was exposed to the lumen and subjected to the loading from blood pressure directly. A high stress concentration appeared in the region without FC (Fig. 3(B)). The stretch ratio could be as high as 2.5, which implied that the deformation was about 150% (Fig. 3(C)). If FC was intact, for the case of intraplaque haemorrhage shown in Fig. 4(A), although high stress concentration appeared in the FC covering the haemorrhage (Fig. 4(B)), the deformation was much smaller (27%

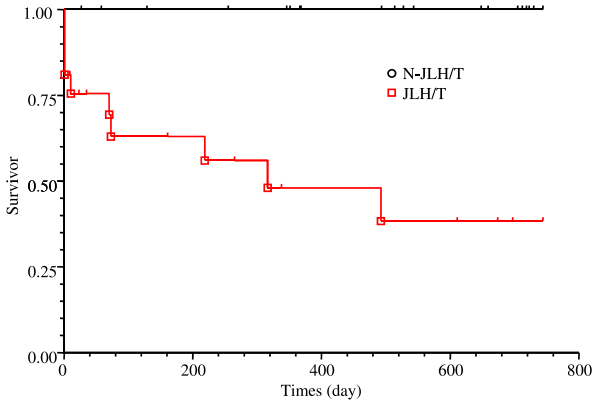

Figure 2 N-JLH/T group has no events during follow up period (black line) whereas JLH/T group is represented by red curve in whom recurrent events were observed. Log rank is p = 0.0001.

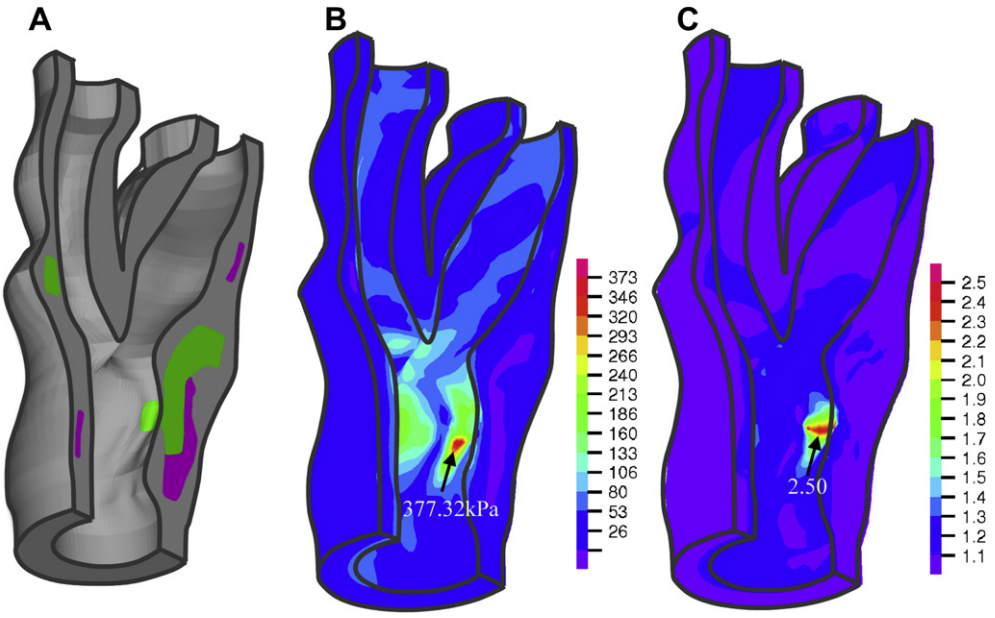

Figure 3 Sagittal cut of plaque with juxtaluminal haemorrhage and band plots of simulation results. (A): initial plaque geometry with the exposure of haemorrhage/thrombosis (green patch on the lumen surface; region marked in magenta stands for the lipid core.); (B): band plot of maximum principle stress (unit: kPa) at systole, showing high stress concentration in the region of exposure of haemorrhage/thrombosis; (C): band plot of maximum principle stretch at systole, showing big deformation in the same region.

for the case shown in Fig. 4(C)). The quantitative comparisons of P-CStress and P-CStretch of both patient groups were visualised in Fig. 5. There is no significant difference in case of P-CStress (Fig. 5(A)) (Mean $\pm$ SD; N-JLH/T: 174.45 $\pm$ 63.96 kPa vs. 212.60 $\pm$ 89.54 kPa; $p = 0.120$), but P-CStretch of JLH/T was significantly bigger than that of N-JLH/T (N-JLH/T: 1.21 $\pm$ 0.08 vs. JLH/T: 2.10 $\pm$ 0.53; $p < 0.0001$).

The variations of stress and stretch were defined as the difference between the peak and valley values during one cardiac cycle. The results indicated that the variation of P-CStress of JLH/T was significantly bigger than that of

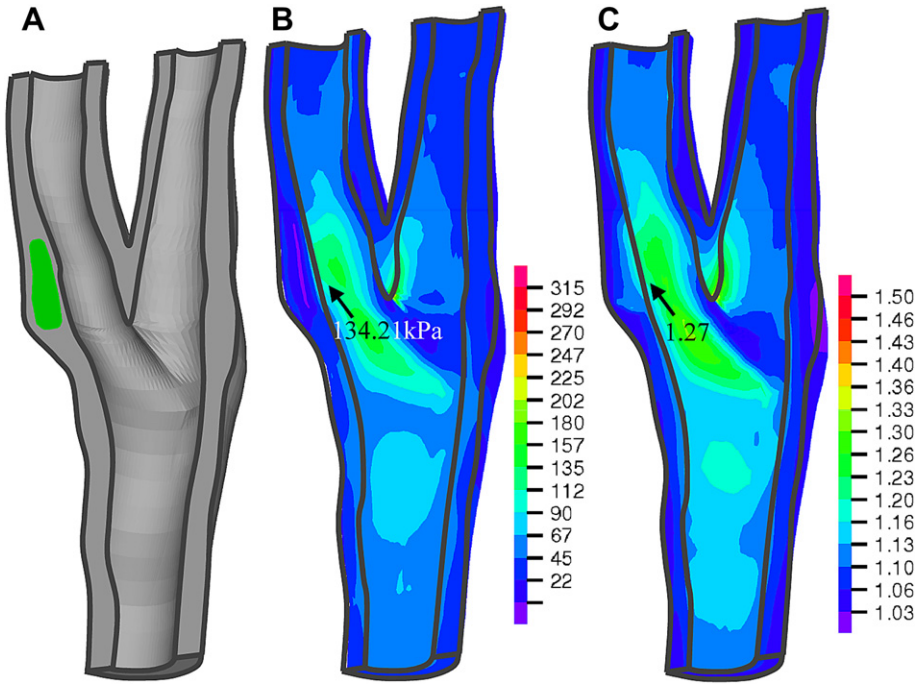

Figure 4 Sagittal cut of plaque with intraplaque haemorrhage and band plots of simulation results. (A): initial plaque geometry (green patch stands for the haemorrhage); (B): band plot of maximum principle stress (unit: kPa) at systole, showing stress concentration appears on the fibrous cap covering haemorrhage; (C): band plot of maximum principle stretch at systole, showing big deformation in the same region.

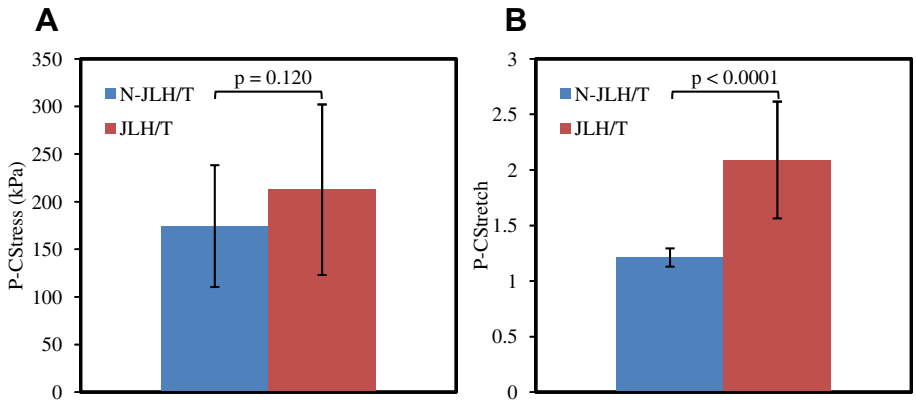

Figure 5 Comparisons of P-CStress and P-CStretch of plaque groups with (JLH/T) and without (N-JLH/T) juxtaluminal haemorrhage/thrombus. (A): no significant difference in the comparisons of P-CStress; (B): the P-CStretch of JLH/T is significantly bigger than that of N-JLH/T.

N-JLH/T (N-JLH/T: 70.55 $\pm$ 39.15 kPa vs. JLH/T: 108.43 $\pm$ 51.33 kPa; $p = 0.010$) and so was the variation of P-CStretch (N-JLH/T: 0.078 $\pm$ 0.040 vs. JLH/T: 0.438 $\pm$ 0.263; $p < 0.0001$).

Discussion

To the best of our knowledge, this is the first study to report, prospectively, the association between the JLH/T and subsequent cerebrovascular events in patients with previous acute symptoms. Mechanical simulations were employed to represent the critical mechanical conditions within the plaque structure. The results indicated that plaques with JLH/T were more likely to cause further events than those without JLH/T. Mechanical analysis showed that the absolute value of stress in both groups was comparable. Although stress condition can differentiate different patient groups,[23–25] results obtained in this study indicate that it is not able to refine risk stratification in the acute symptomatic patient group, while degree of deformation can. The stretch in the patient group with JLH/T was much bigger than that of the patient group without JLH/T.

Stress, and particularly stretch, of the JLH/T group, experienced much bigger variations during one cardiac cycle. It suggested that bigger deformation of the plaque structure indicated a higher risk of a patient experiencing further events, as it is in agreement with the clinical observations using ultrasound. It has been shown that the maximum discrepant surface velocity, defined as the maximum of differences between maximum and minimum surface velocities in symptomatic plaque, was significantly higher than that of asymptomatic plaque[26] and mobile plaque (bigger movement during a cardiac cycle) is associated with increased risk of ischaemic stroke.[27]

Although the stress level in these two groups is comparable, 11 out of 21 (52.4%) plaques with JLH/T have P-CStress appearing over the surface of haemorrhage/thrombus. Such stress levels (about 200 kPa, as shown in Fig. 5(A)) may tear the haemorrhage/thrombus clot from the host plaque structure and cause thrombotic events, as haemorrhage/thrombus is a much weaker material compared with FC (Young's modulus of haemorrhage/thrombus is about 10 kPa for fresh and 80 kPa for chronic[28] and that of FC is about a few thousand kPa).[29,30] Moreover, P-CStretch of JLH/T are all located over the surface of exposed haemorrhage/thrombus. Such big deformation may regulate the expression of cytoskeletal genes, such as filamin A,[31] effecting cell attachment and programming local cell apoptosis[32–34] and therefore impeding healing by preventing the formation of new FC.

Despite the interesting finding obtained in this study, limitations exist: (1) the validation of MRI finding was not done as this has been validated previously[4,6,13] and (2) the patient-specific material properties were not used in simulations, as they are not currently measureable with non-invasive techniques and the residual stress was not considered for the same reason.[35]

Conclusively, MRI-depicted JLH/T might be a high risk factor for identifying plaques associated with recurrent cerebrovascular events in TIA patients. Big deformation and large variations of stress and stretch during a cardiac cycle might be responsible for the thrombotic events in TIA patients with JLH/T.

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Disclosure

None.

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